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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/181,108	10/28/1998	BENJAMIN L. MILLER	176/60440-(1	9507

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EXAMINER

CELSA, BENNETT M

ART UNIT

PAPER NUMBER

1627

DATE MAILED: 07/05/2002 24.

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

# Office Action Summary

Application No.  
09/181,108

Applicant(s)  
Miller et al.

Examiner  
Bennett Celsa

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1627



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Apr 22, 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 10 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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## **DETAILED ACTION**

### ***Continued Prosecution Application***

1. The request filed on 4/22/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/181,108 is acceptable and a CPA has been established. An action on the CPA follows.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Status of the Claims***

Claims 1-7 and 10 are pending and under consideration.

### ***Election/Restriction***

3. Applicant's election of Group I (original claims 1-10), with traverse in paper No. 10 and applicant's further election, without traverse, of the species of bis-N-[2-(2-aminomethyl)-1-methyl pyrrolidine]salicyladimanate Zinc II in Paper No. 13 which reads on claims 1-7 and 10 in response to the Supplemental Election of Species in paper no. 11 is again acknowledged.
4. It is noted that the prior obvious rejection of the over Barton US Pat. No. 4,980,473 (12/90) and Benner, U.S. Pat. No. 5,958,702 (9/99: filed 2/95) has been withdrawn, without prejudice in lieu of the use of the more appropriate Barton '032 reference below.
5. Upon further consideration, the 102/103 rejection over the Jacobsen WO reference is withdrawn in lieu of the new 103 rejection including this reference, cited below.

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***Claim Rejections - 35 USC § 102 and 35 USC § 103***

5. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Huc et al. PNAS USA Vol. 94 pages 2106-2110 (3/97).

The general application of "Receptor Assisted Combinatorial Chemistry" to generate libraries of "reversible" complexes for receptor screening in equilibrium under "physiological conditions" (e.g. aqueous) is taught by the Huc et al. reference (e.g. See Abstract and for aqueous environment: see Huc et al. at page 2107 right column: "reaction on which the library is based ... physiological conditions ... equilibrate in presence of receptor"; and on page 2108, left column in which the CA enzyme is present "in water at pH6"). For example, Huc et al. teach the making and screening (e.g. using "receptor-induced assembly" : see abstract and fig. 1) of a combinatorial library of "reversible" "labile" bonded complexes of "a plurality of at least six different complexes" (e.g. greater than or equal to 24 complexes: 4x6 plus enantiomers) under "physiological conditions" (e.g. in aqueous solution or suspension in equilibrium) in the presence of "a biological receptor" (e.g. a transition metal  $Zn^{+2}$  & carbonic anhydrase: CAII) in which 4 or more amine ligands (e.g. a-d in Fig. 2) and 6 or more aldehyde/alcohol ligands are present in aqueous solution in the presence of CAII (e.g.  $Zn^{+2}$  and carbonic anhydrase). See Fig. 1-2; page 2107-2108. Such a technique results in the generation of large libraries which are most easily screened in solution.

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6. Claims 1-7 and 10 are rejected under 35 U.S.C. 103(a) as obvious over Huc et al. PNAS USA Vol. 94 pages 2106-2110 (3/97) alone or further in view of Benner, U.S. Pat. No. 5,958,702 (9/99: filed 2/95).

The general application of "Receptor Assisted Combinatorial Chemistry" to generate libraries of "reversible" complexes for receptor screening in equilibrium under "physiological conditions" (e.g. aqueous) is taught by the Huc et al. reference (e.g. See Abstract and for aqueous environment: see Huc et al. at page 2107 right column: "reaction on which the library is based ... physiological conditions ... equilibrate in presence of receptor"; and on page 2108, left column in which the CA enzyme is present "in water at pH6"). For example, Huc et al. teach the making and screening (e.g. using "receptor-induced assembly" : see abstract and fig. 1) of a combinatorial library of "reversible" "labile" bonded complexes of "a plurality of at least six different complexes" (e.g. greater than or equal to 24 complexes: 4x6 plus enantiomers) under "physiological conditions" (e.g. in aqueous solution or suspension in equilibrium) in the presence of "a biological receptor" (e.g. a transition metal  $Zn^{+2}$  & carbonic anhydrase: CAII) in which 4 or more amine ligands (e.g. a-d in Fig. 2) and 6 or more aldehyde/alcohol ligands are present in aqueous solution in the presence of CAII (e.g.  $Zn^{+2}$  and carbonic anhydrase). See Fig. 1-2; page 2107-2108. Such a technique results in the generation of large libraries which are most easily screened in solution. .

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The Huc et al. reference libraries differs from the presently claimed invention insofar that the presently claimed invention “collects together” (e.g. combinatorializes) in libraries of “at least 100 different complexes” (e.g. see present claim 10)

However, the Huc et al. reference motivates one of ordinary skill in the art to generate “all possible combinations of a set of basic components, thus making virtually available all structural and interactional features that these combinations may present” (e.g. see Huc et al. Page 2106). Accordingly, the Huc et al. provides explicit motivation to scale up the library by increasing the number of ligands (e.g. aldehyde and/or amine ligands) and form bigger libraries in order to generate and screen better receptor binding compounds (e.g. see abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant’s invention to “scale up” the Huc et al. Library and obtain “at least 100 different complexes” within the scope of the presently claimed invention.

Additionally, the Benner reference discloses the advantages of utilizing soluble “combinatorial library” techniques for generated diverse structures which could then be advantageously screened e.g. using a “receptor-assisted combinatorial chemistry” (e.g. see col. 2-5).. In this regard, the Benner reference discloses the versatility of this approach as utilized over a wide range of complexed atoms, groups of atoms or ions. In this regard, the Benner reference discloses the use of biopolymer or non-biopolymer ligands

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant’s invention to “scale up” the Huc et al. Library and obtain “at least 100 different

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complexes” within the scope of the presently claimed invention as suggested by the Huc reference teaching alone or in view of the Benner reference teaching.

7. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bruno et al. US Pat. No. 5,976,887 (11/99: filed 6/97) in view of the specification (e.g. page 10) cited in order to demonstrate the presence of functional properties inherent to the disclosed reference ligands. See MPEP 2131.01(d) which permits the citation of references or evidence in an anticipation rejection under 35 U.S.C. 102 in order to show that a characteristic not disclosed in the reference is inherent.

Bruno discloses the formation of combinatorial metal/ligand library complexes comprising aqueous equilibrium mixtures (e.g. see presence of deionized water in assay of example 1; or source of (transition) metal ions being wastewater, sewage etc: col. 1 and patent claims) of 3 or more diaminoaromatic ligands (e.g. see 2/4 diaminotoluene; 3/4 diaminotoluene; 2/3 diaminotoluene: e.g. see patent claims 1, ) and one or more metals (especially transition metals) (e.g. Au, Cu, Cr, Fe, Ru, Se and Va) to form combinatorial libraries of reversible metal/ligand complexes. The reference disclosure of the use of 17 metal ions (e.g. see Table 1) with two separate generics of substituted (with R)/unsubstituted diamino phenyl and substituted (with R)/unsubstituted naphthyl ligands would immediately envisage (e.g. anticipate) or in the alternative render obvious the making of a library of complex of 100 or greater [e.g. 17x 6(or more) phenyl ligands x 6(or more)naphthal ligands ]. The formation of the metal reference

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complex ensure that the reference ligands possess “at least one functional group capable of bonding to the metal atom” (e.g. an amino group). Additionally, all of the reference ligands inherently contain either unsubstituted or substituted (e.g. with amino or R) phenyl groups and thus comprise “a recognition group capable of binding a biological receptor” since recognition elements (e.g. DNA intercalators) include “substituted or unsubstituted phenyl groups” (e.g. see specification page 10, lines 4-5). Additionally, the reference ligands are “capable” of being modified to contain “recognition groups” within the scope of the presently claimed invention and thus would “comprise a recognition group *capable of* binding a biological receptor”. It is noted that the reference complexes (e.g. see reference figures 1-13, especially figure 13) encompass the formation of complexes within the structural formula of present claims 1-7 and thus would be expected to inherently possess “a rate constant of greater than about 2 per second” since complexation does occur preferentially with the binding of 3 ligands/metal. However, in this regard it is noted that the Patent Office lacks the facilities for making comparisons between prior art and reference reaction kinetics; thus shifting the burden to applicant who is better able to make such comparisons.



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8. Claims 1-7 and 10 are rejected under 35 U.S.C. 103(a) as obvious over Jacobsen et al. WO 98/12156 (3/98) in view of Huc et al. PNAS USA Vol. 94 pages 2106-2110 (3/97) alone or if necessary further in view of Benner US Pat. No. 5,958,702 (9/99) ...

Jacobsen et al. disclose a combinatorial approach for generating novel coordination complex mixtures of "at least 6" (e.g. see page 6, lines 5-10) by coordinating to a transition metal (e.g. including zinc: see e.g. Page 6, lines 17-26) and ligands (e.g. non-biopolymer: see e.g. pages 25-31) to form bidentate, tridentate, tetradentate or even higher order metal chelating ligands (e.g. see page 6, lines 7-10; and abstract). Additionally, a large number of the reference ligands (e.g. see pages 25-31) comprise substituted and unsubstituted aryl and heterocyclic moieties which would constitute "recognition elements" that are capable of being classed as "DNA intercalators" or "major or minor groove DNA binders" within the open ended specification definition of these terms (e.g. see specification pages 7-10 which encompass aryl and heterocycles as well as "hydroxy"; "alkoxy" or "amine" groups which are within the scope of the presently claimed invention ) with these ligands being either phenyl or substituted derivative which further comprise an amine moiety. Alternatively, the selection of such an intercalating ligand would be obvious to one of ordinary skill in the art. See e.g. reference claims 29-30 and Fig. 1-11 disclose specific reference library combinations which are within the scope of the presently claimed invention.

Additionally, the Jacobsen reference also teaches that the reaction of the metal(s) with the library of PBM to form a combinatorial library of potential catalysts comprising metal complexes

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can occur in "solution", on a soluble support or utilizing insoluble polymeric supports (e.g. see page 39).

The Jacobsen reference making and screening of combinatorial solution phase library metal complexes differs from the presently claimed invention insofar that the presently claimed invention forms combinatorial libraries of complexes, such as those in Jacobson, in aqueous solution using "Receptor Assisted Combinatorial Chemistry" (aka RACC)..

The general application of "Receptor Assisted Combinatorial Chemistry" to generate libraries of "reversible" complexes for receptor screening in equilibrium under "physiological conditions" (e.g. aqueous) is taught by the Huc et al. reference (e.g. See Abstract and for aqueous environment: see Huc et al. at page 2107 right column: "reaction on which the library is based ... physiological conditions ... equilibrate in presence of receptor"; and on page 2108, left column in which the CA enzyme is present "in water at pH6"). For example, Huc et al. teach the making and screening (e.g. using "receptor-induced assembly" : see abstract and fig. 1) of a combinatorial library of "reversible" "labile" bonded complexes of "a plurality of at least six different complexes" (e.g. greater than or equal to 24 complexes: 4x6 plus enantiomers) under "physiological conditions" (e.g. in aqueous solution or suspension in equilibrium) in the presence of "a biological receptor" (e.g. a transition metal  $Zn^{+2}$  & carbonic anhydrase: CAII) in which 4 or more amine ligands (e.g. a-d in Fig. 2) and 6 or more aldehyde/alcohol ligands are present in aqueous solution in the presence of CAII (e.g.  $Zn^{+2}$  and carbonic anhydrase). See Fig. 1-2; page

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2107-2108. Such a technique results in the generation of large libraries which are most easily screened in solution. .

Additionally,, the Benner reference discloses the advantages of utilizing soluble “combinatorial library” techniques for generated diverse structures which could then be advantageously screened e.g. using a “receptor-assisted combinatorial chemistry” (e.g. see col. 2-5).. In this regard, the Benner reference discloses the versatility of this approach as utilized over a wide range of complexed atoms, groups of atoms or ions. In this regard, the Benner reference discloses the use of biopolymer or non-biopolymer ligands

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant’s invention to apply RACC to the Jacobson transition metal and ligands (e.g. phenanthroline etc.) Libraries to generate complexes which contain “recognition elements” that are “capable of” binding a “target molecule” in solution (e.g. aqueous sol’n or suspension) in view of the advantages of utilizing combinatorial techniques (e.g. increasing diversity) in solution (e.g. aqueous) as well as the advantages of utilizing improved screening techniques (e.g. receptor-assisted combinatorial chemistry) as disclosed in the Huc et al. reference taken alone or further in view of the Benner reference teaching.

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9. Claims 1-7 and 10 are rejected under 35 U.S.C. 103(a) as obvious over Barton US Pat. No. 5,157,032 (10/92) in view of Huc et al. PNAS USA Vol. 94 pages 2106-2110 (3/97) alone or if necessary further in view of Benner US Pat. No. 5,958,702 (9/99).

Barton discloses (chiral) reversible coordination complexes of transition metals which comprise "at least two non-biopolymer ligands" (e.g. three ligands which comprise unsubstituted/substituted 1,10 phenanthrolines, racemers and isomers) which contain a "recognition element" which "targets" DNA (e.g. see abstract, examples and patent claims, especially patent claim 1). For example, Barton discloses a cobalt complex with ligands which comprise 1,10 phenanthroline and a list of 12 "substituted" phenanthrolines" (e.g. hydroxy, phenyl, substituted phenyl intercalators etc.) which include their racemers (e.g. see col. 7, lines 1-40) which would encompass at least 169 distinct complexes (e.g. 13x13 representing 13 unsubstituted and substituted and their D/L enantiomers). These complexes are then screened for their binding to a "receptor" (e.g. DNA) by intercalation: see. bottom of col. 7 to top of col. 8).

The Barton reference composition differs from the presently claimed invention insofar that the presently claimed invention forms combinatorial libraries of complexes, such as those in Barton, in aqueous solution using "Receptor Assisted Combinatorial Chemistry" (aka RACC)..

The general application of "Receptor Assisted Combinatorial Chemistry" to generate libraries of "reversible" complexes for receptor screening in equilibrium under "physiological conditions" (e.g. aqueous) is taught by the Huc et al. reference (e.g. See Abstract and for aqueous environment: see Huc et al. at page 2107 right column: "reaction on which the library is

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based ... physiological conditions ... equilibrate in presence of receptor”; and on page 2108, left column in which the CA enzyme is present “in water at pH6”). For example, Huc et al. teach the making and screening (e.g. using “receptor-induced assembly” : see abstract and fig. 1) of a combinatorial library of “reversible” “labile” bonded complexes of “a plurality of at least six different complexes” (e.g. greater than or equal to 24 complexes: 4x6 plus enantiomers) under “physiological conditions” (e.g. in aqueous solution or suspension in equilibrium) in the presence of “a biological receptor” (e.g. a transition metal  $Zn^{+2}$  & carbonic anhydrase: CAII) in which 4 or more amine ligands (e.g. a-d in Fig. 2) and 6 or more aldehyde/alcohol ligands are present in aqueous solution in the presence of CAII (e.g.  $Zn^{+2}$  and carbonic anhydrase). See Fig. 1-2; page 2107-2108. Such a technique results in the generation of large libraries which are most easily screened in solution. ...

Additionally, the Benner reference discloses the advantages of utilizing soluble “combinatorial library” techniques for generated diverse structures which could then be advantageously screened e.g. using a “receptor-assisted combinatorial chemistry” (e.g. see col. 2-5).. In this regard, the Benner reference discloses the versatility of this approach as utilized over a wide range of complexed atoms, groups of atoms or ions. In this regard, the Benner reference discloses the use of biopolymer or non-biopolymer ligands

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant’s invention to apply RACC to the Barton generic of transition metal and ligands (e.g. phenanthroline etc.) to generate complexes which contain “recognition elements” that are

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“capable of” binding a “target molecule” (e.g. DNA) in solution (e.g. aqueous sol’n or suspension) in view of the advantages of utilizing combinatorial techniques (e.g. increasing diversity) in solution (e.g. aqueous) as well as the advantages of utilizing improved screening techniques (e.g. receptor-assisted combinatorial chemistry) as disclosed in the Huc et al. reference taken alone or further in view of the Benner reference teaching.

Additionally, scaling the library up by increasing the number of library members (e.g. increase the number of Barton substituted phenanthroline ligand) to attain increased diversity is suggested by both the Huc et al. And Benner references, taken separately or in combination, and would in any event represent mere optimization to one of ordinary skill in the art.

**General information regarding further correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

July 3, 2002

**BENNETT CELSA**  
**PRIMARY EXAMINER**

